Pharmacology of Cannabinoids

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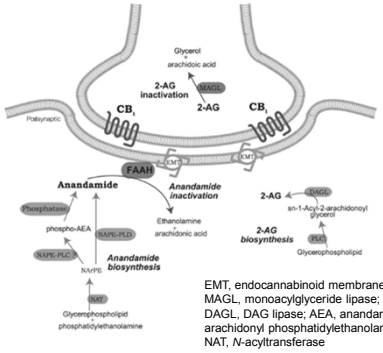
Endocannabinoid system in pre- and postsynaptic neurons



EMT, endocannabinoid membrane transporter; MAGL, monoacylglyceride lipase; DAGL, DAG lipase; AEA, anandamide; NArPE, *N*-arachidonyl phosphatidylethanolamine; NAT, *N*-acyltransferase

Pharmacol Rev. 2006; 58(3): 389–462

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Chemical structure and pharmacological activity of endogenous cannabinoids

Anandamide (AEA)	CB_1 >> CB_2 agonist $TRPV_1$ agonist	Mechoulam et al., 1995 Khanolkar et al., 1996 Schowalter et al., 1996 Felder et al., 1995 Zygmunt et al., 1999
2-Arachidonoyl glycerol (2-AG)	$CB_1 \approx CB_2$ agonist	Mechoulam et al., 1995 Ben-Shabat et al., 1998
2-Arachidonoyl glycerol ether	CB_1 >> CB_2 agonist	Hanus et al., 2001
O-Arachidonoyl ethanolamine (virodhamine)	CB_1 >> CB_2 agonist	Porter et al., 2002
N-Arachidonoyl dopamine	CB_1 >> CB_2 agonist $TRPV_1$ agonist	Bisogno et al., 2000 Huang et al., 2002

Pharmacol Rev 2006; 58(3): 389–462

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Important features of endocannabinoids

- Synthesized on demand eg. brain trauma
- Act locally (paracrine or autocrine)
- Quickly degraded after their action
- Act as retrograde neurotransmitters in the nervous system
- Inhibit neurotransmitter release
- Derived from lipid precursors

Devane et al 1992; Sugiura et al 1995; Schmid 2000; Howlett et al 2004; Hillard et al 2000; Alger 2002

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The EC System Is a General Stress-Recovery System and Is Overall "Silent"; It Becomes Transiently Activated To:

Relax

reduction of pain and anxiety; modulation of body temperature, hormone production, smooth muscle tone, and blood pressure

Rest

inhibition of motor behavior and sedation

Forget

extinction of aversive memories

Protect

at both the cellular and emotional levels

Eat

appetite-inducing and reward-reinforcing effects

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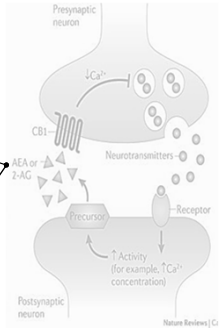
Pharmacology of cannabinoids

Phytocannabinoids

Endocannabinoids



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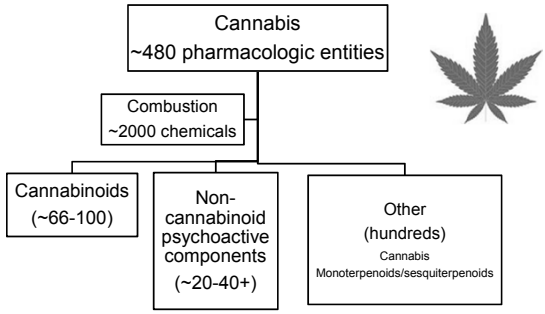
Historical comparisons between cannabinoids and opioids

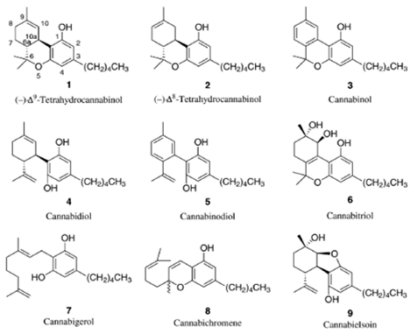
Pharmacological Discoveries	Cannabinoids	Opiates
Discovery of receptor existence	1988 (Devane et al. and Dill and Howlett)[36,40]	1973 (Pert and Snyder, Simon, and Terenius)[123,149,162]
Identification of receptor antagonist	1994 SR 141716A (Rinaldi-Carmona et al.)[132]	Before 1973: naloxone
Discovery of first endogenous ligand	1992 anandamide (Devane et al.)[37]	1975 met- and leu-enkephalin (Hughes et al.)[70]
First receptor cloned	1990 (Matsuda et al.)[107]	1992 (Evans et al. and Kieffer et al.)[41,82]
Natural functions	Unknown	Pain, reproduction, mood, movement, and others

More than 400 compounds in Cannabis



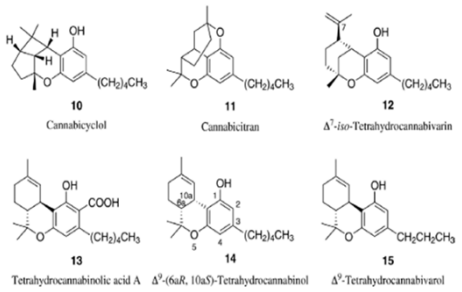
The composition of cannabis varies depending upon species (*C. sativa, C. indica, C. ruderalis)*,geography,locations and growth manipulations

Chemical structures of main phytocannabinoids isolated from *Cannabis sativa L.*



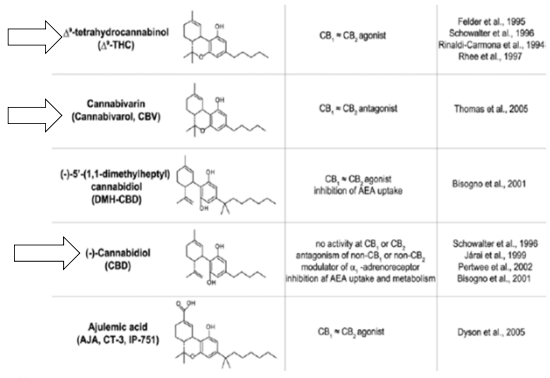
http://dx.doi.org/10.1016/B978-0-12-800756-3.00068-5

Chemical structures of main phytocannabinoids isolated from *Cannabis sativa L.* (cont)



http://dx.doi.org/10.1016/B978-0-12-800756-3.00068-5

Chemical structure and pharmacological activity of phytocannabinoids



Pharmacol Rev 2006; 58(3): 389–462

Not all cannabinoids are psychoactive

Cannabinoids	
Psychoactive	Not Psychoactive
• Cannabinol (CBN) • Cannabinodiol (CBDL) • delta – 9 –/delta-8 tetrahydrocannabinol (THC)	• Cannabigerols (CBG) • Cannabichromenes (CBC) • Cannabidiols (CBD)

http://learnaboutmarijuanawa.org/factsheets/cannabinoids.htm

Cannabinoids pharmacological actions

	THC (delta-9-tetrahydro-cannabinol)	CBD (Cannabidiol)	CBN (Cannabinol)
Psychoactive	√		√
Anti-emetic	√		
Appetite stimulant	√		
Analgesic	√	√	
Anti-inflammatory		√	√
Anti-seizure		√√	√
Anti-spasmodic		√	
Neuroprotective		√	

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Molecular mechanisms of phytocannabinoids

- **Activity at cannabinoid receptors**
- **Cannabinoid receptor independent activity**

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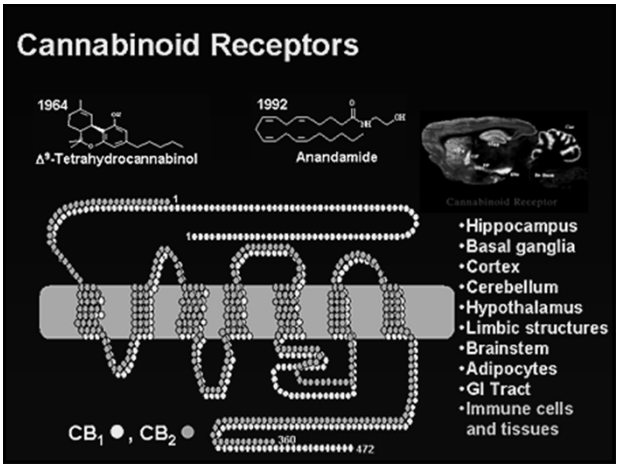
Cannabinoid Receptors



Location of cannabinoid receptors

Location	Structure	Function
CB_1 receptors		
CNS	Hippocampus	Memory storage
	Cerebellum	Coordination of motor function, posture, balance
	Basal ganglia	Movement control
	Hypothalamus	Thermal regulation, neuroendocrine release, appetite
	Spinal cord	Pain
	Vomiting center/ N tractus solitarius	Emesis
Periphery	Lymphoid organs	Cell-mediated and innate immunity
	Vascular smooth muscle cells	Control of blood pressure
	Duodenum, ileum, myenteric plexus	Control of emesis
	Lung smooth muscle cells	Bronchodilation
	Eye ciliary body	Intraocular pressure
CB_2 receptors		
Periphery	Lymphoid tissue	Cell-mediated and innate immunity
	Peripheral nerve terminals	Peripheral nervous system
	Retina	Intraocular pressure
CNS	Cerebellar granule cells mRNA	Coordination of motor function

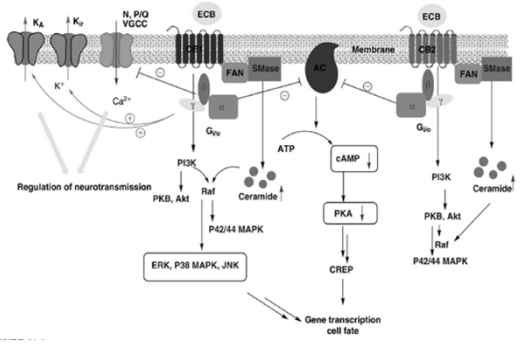
16 Croxford, JL. CNS Drugs 2003; 17(3)

Signal Transductions of CB1 and CB2 Receptors

- Coupled with Gi therefore suppresses adenylyl cyclase and downregulates signaling responses mediated by second messenger c-AMP
- CB1 receptor inhibits N/P/Q-type voltage-gated Ca2+ channels and activates A-type and G-protein-coupled inwardly-rectifying K+ channels (GIRK)
- Both the CB1 and CB2 cannabinoid receptors regulate the phosphorylation and activation of different members of all three families of mitogen-activated protein kinases (MAPKs), including p44/42 MAP kinase, p38 kinase, and JUN-terminal kinase

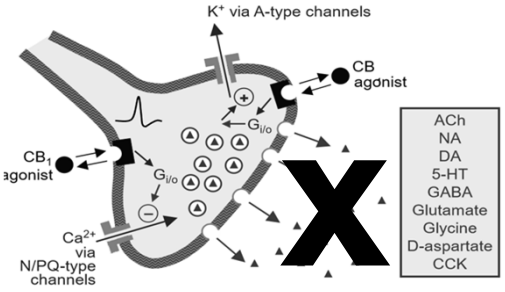
17 http://dx.doi.org/10.1016/B978-0-12-800756-3.00068-5

Major signaling pathways initiated from activation of the cannabinoid CB1 and CB2 receptors



18 http://dx.doi.org/10.1016/B978-0-12-800756-3.00068-5

CB1 receptor signal transduction



Howlett (2002); Pertwee (2005a)

CB1 receptor inhibits N/P/Q-type voltage-gated Ca2+ channels and activates A-type and G-protein-coupled inwardly-rectifying K+ channels (GIRK)

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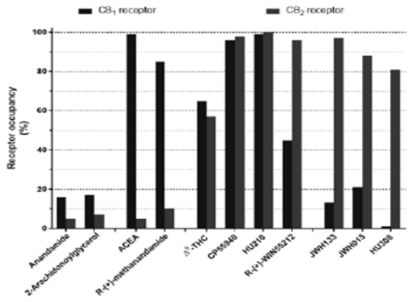
Selectivity of some endogenous, plant-derived and synthetic cannabinoids



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Brain and Neuroscience Advances 2018; 2: 1–8

Some Ki values of (-)-D9-THC and certain other phytocannabinoids

Phytocannabinoid	CB_1 K_i (nM)	CB_2 K_i (nM)
(−)-Δ^9-THC	5.05	3.13
	35.3[a]	3.9[a]
	39.5[b,c]	40[c]
	21	36.4
	53.3	75.3
	80.3[b,c]	32.2[c]
(−)-Δ^8-THC	44[a]	44
	47.6[a]	39.3[d]
(−)-Δ^9-THCV	75.4[d]	62.8
	46.6[d]	ND
Cannabinol	120.2	100
	211.2[b,c]	126.4[c]
	326	96.3
	1130	301
CBD	4350[a]	2860
	4900[d]	4200
	27 542	2399
	>10 000[a,c]	>10 000[c]
Cannabigerol	440[d]	337

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British Journal of Pharmacology 2008; 153, 199–215

CB1 receptor effects

Physiologic effects

- CNS depressant effects (drowsiness, decrease alertness, slow reaction, impair short term memory, decreased accuracy of psychomotor task performance, motor coordination and muscle tone

Psychologic effects

- Low dose: Elation, euphoria, decrease anxiety, increased appetite, heightened perception
- High dose: Dysphoria, increase anxiety, irritability, impaired short term memory, hallucination, panic reaction, paranoia, sensory distortions

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Baron EP. Headache. June 2015

Chronic Effects

- **CNS**
  - **Cognitive and executive decline: poor memory, vagueness of thought, decreased verbal fluency, learning deficits**
  - **daily high doses can cause chronic intoxication syndrome (apathy), confusion, depression, paranoia**
  - **cannabis dependence (DSM-V criteria)**

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Chronic cannabis exposure

- **Cannabinoid tolerance dvelops in the absence of pharmacokinetic changes**
- **CB1 receptor downregulation following chronic cannabis exposure (confirmed in human using PET)**
- **Significant reduction in cortical region but not in noncortical areas**

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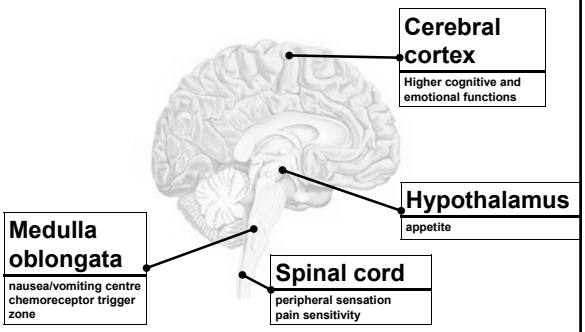
Molecular Psychiatry 2012;17: 642-9

CB1 receptor distribution



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delta -9 - tetrahydrocannabinol (THC) – Sites of Action

- THC activates CB1 receptors all over the brain
- Some possible sites of action
  - Cerebral cortex/ Hippocampus - memory impairment
  - Nucleus accumbens - euphoria/psychosis (increased DA release)
  - Hypothalamus - stimulation of appetite
  - Vomiting center – antiemetic action
  - Spinal cord – analgesic effect

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Brain Reward Pathway

- *Mesolimbic dopamine pathway*

  project from ventral tegmental area (VTA) to the nucleus accumbens (NAcc) shell region

- *Mesocortical dopamine pathway*

  project from ventral tegmental area (VTA) to the prefrontal cortex

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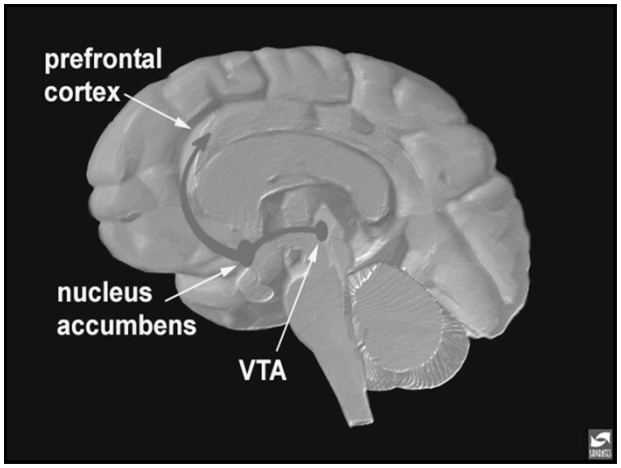
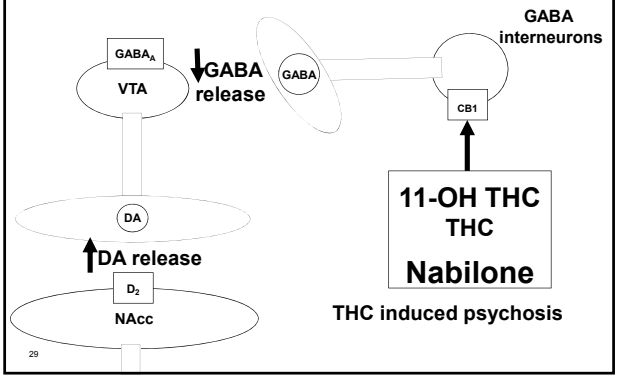


Effect of THC on DA release at NAcc



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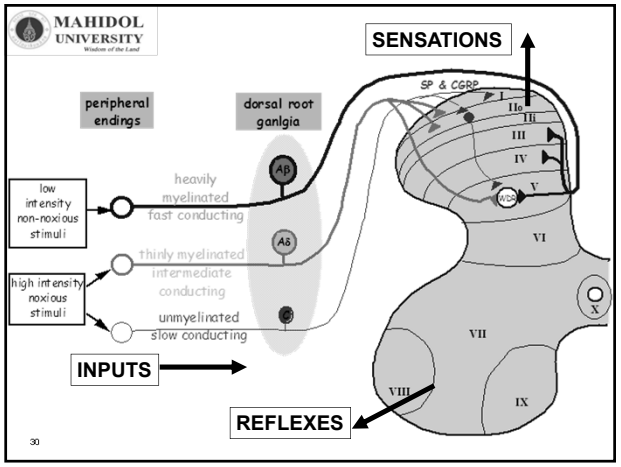

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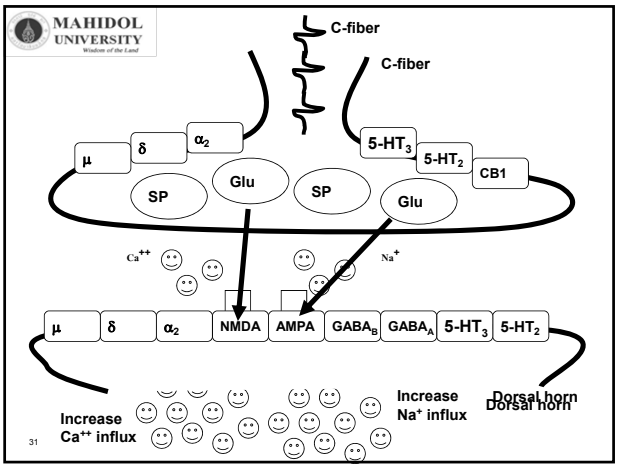

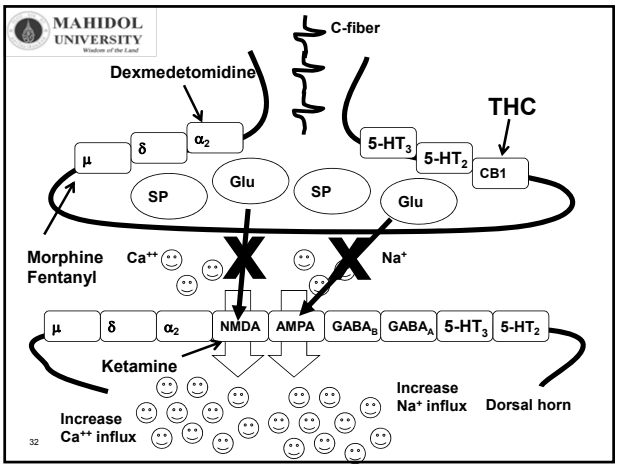

THC action independent of CB1 and CB2 receptors

- At < 1 uM THC can activate GPR18, GPR55, PPARγ, TRPV2 and TRPA1 receptor
- THC block the activity of 5-HT3 receptors (antiemetic effects) and TRPM8 receptors at concentration < 1 uM

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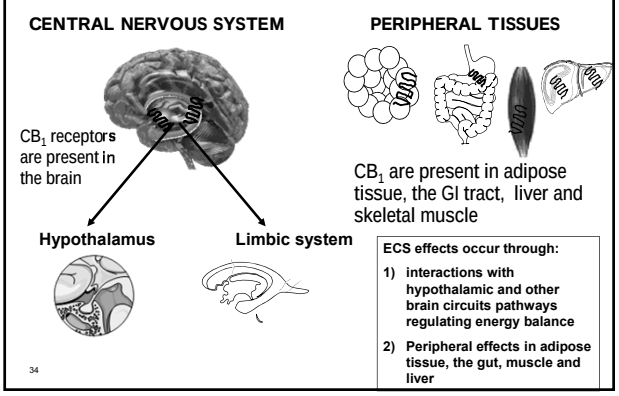
Central and peripheral targets of the endocannabinoid system (ECS)



Sites of CB_1 receptor and effects of CB_1 receptor antagonist (eg. rimonabant)

	Site of Action	Mechanisms	Effects
	Hypothalamus / Nucleus accumbens	↓ Food intake	Body weight Intra abdominal adiposity
	Adipose tissue	↑ Adiponectin ↓ Lipogenesis	Dyslipidemia Insulin resistance
	Muscle	↑ Glucose uptake	Insulin resistance
	Liver	↓ Lipogenesis	Dyslipidemia Insulin resistance
	GI tract	↑ Satiety signals	Body weight Intra abdominal adiposity

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DiMarzo 2001; Ravinet Trillou et al 2003; Cota et al 2003; Pagotto et al 2005; Van Gaal et al 2005; Liu et al 2005; Osei-Hyiaman et al 2005

THC/CB1 Drugs – Current medical use

- Agonists (cannabis, dronabinol, nabilone)
  - Anti-emetic (chemotherapy)
  - Appetite stimulant (AIDs)
  - Analgesic (neuropathic pain, multiple sclerosis)

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CBD pharmacology: "Multitarget"

- Cannabidiol has low affinity for both cannabinoid CB1 and CB2 receptors (negative allosteric moderator of CB1)
- CBD has agonist effect at the 5-HT1A receptor, the $\alpha 3$ and $\alpha 1$ glycine receptors and TRPV1
- Moderately inhibit cellular reuptake of anandamide
- Moderate inhibitor of anandamide hydrolysis by FAAH
- At low micromolar to sub-micromolar concentrations, CBD is a blocker of the equilibrative nucleoside transporter (ENT), the orphan G-protein-coupled receptor GPR55, and the transient receptor potential of melastatin type 8 (TRPM8) channel
- Potent antioxidant

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Rambam Maimonides Med J 2013;4 (4):e0022. doi:10.5041/RMMJ.10129; Epilepsia, 55(6):791–802, 2014

CBD pharmacology: "Multitarget"

- Negative allosteric moderator of CB1: reduce unwanted effect of THC
- 5-HT1A receptor agonist: anxiolytic effect, analgesic effect
- Glycine receptors agonist: anti-seizure, antispasmodic
- Increase anandamide: anxiolytic effect, analgesic effect, anti-seizure

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Anti-Seizure Effects of CBD – Animal Studies

- **Active in the MES, MET and 6Hz ECS models.**
- **Broad spectrum**
- **Promising clinical effects in epilepsy**

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CBD has anti-inflammatory effects

- **Increase adenosine stimulation at A1A and A2A adenosine receptors via the inhibition of adenosine uptake by equilibrative nucleoside transporter (ENT1)**
- **Activation of strychnine-sensitive α1 and α1β glycine receptors**
- **CBD dose-dependently suppressed the production and secretion of both IL-17 and of IL-6, a key factor in Th17 induction**

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Eur J Pain 2018; 22: 471-84
J Basic Clin Physiol Pharmacol 2016; 27(3): 181–7

Cannabinoid hyperemesis syndrome (CHS)

- Clinical entity characterized by chronic marijuana use with intractable vomiting
- TRPV1 is expressed in area postrema of the medulla, along gastric enteric and vagal nerves, and on cutaneous receptors in the dermis and epidermis.
- **delta-9-tetrahydrocannabinoil, activate both CB1 and TRPV1**
- Prolonged exposure to cannabinoids inactivates TRPV1, potentially resulting in central nausea, altered gastric motility, and abdominal pain.
- Exposure to nociceptive heat, such as with compulsive hot-water bathing, may transiently augment cutaneous TRPV1 firing and restore gastric motility, temporarily mitigating symptoms.
- Use of another TRPV1 agonist, capsaicin, may also provide relief.
- Cessation ofmarijuana use gradually leads to normalization of TRPV1 function and fully ameliorates symptoms

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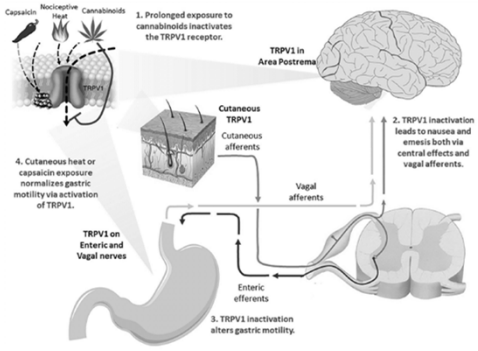
ACG Case Rep J 2018;5:e3

Proposed pathophysiology of cannabinoid hyperemesis syndrome



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ACG Case Rep J 2018;5:e3

Cannabinoid pharmacokinetics

Pharmacokinetic parameters	Clinical Implications
• Very lipophilic • THC: Vd = ~10L/kg	• Distributes into tissues • Long duration of effect • Safety concerns in pregnancy and lactation
• Hepatic metabolism (CYP3A4, 2C9, 2C19, 2D6)	• High first pass effect • Genetic variability • Many drug interactions
• Long half-life and many active metabolites (THC: ~25-36h; tissue 5-7d) • Elimination over days to weeks, hundreds of metabolites, via urine and feces	• Long duration of effect • Natural taper when discontinued • Prolonged exposure to toxins • Affects timing of monitoring

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CBD drug interactions

- **Inhibit CYP1A2, CYP2B6, CYP2C9, CYP2D6, and CYP3A4**
- **Inhibits p-glycoprotein**
- **Enhance CNS depressant effects when coadministration with other CNS depressant drugs**

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Cannabis products in the market

Products can vary greatly in active substances and their concentration

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Pharmaceutical products

GW Pharmaceuticals (UK)

Sativex: THC:CBD extract
Prescription medicine
Admin: sublingual spray

Epidiolex: CBD
Admin: oral dose

Bedrocan BV (NT)

Bedrocan: GMP cannabis flos
Prescribed medicine (NL)
Admin: vaporization (oral dose forms also available)

AbbVie Inc. (USA)

Marinol: synthetic THC (Dronabinol)
Prescription medicine
Admin: oral dose

Valeant Pharma. Int. (USA)

Cesamet: synthetic THC (Nabilone)
Prescription medicine
Admin: oral dose

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Cannabinoids in palliative care setting

- **Reduce pain**
- **Relaxation**
- **Increase appetite**
- **Reduce vomiting & nausea**

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Cannabis – the Israeli perspective

- Not all medical conditions can be treated with the same ratio of cannabis constituents or with pure compounds.
- In epilepsy, pure CBD is apparently preferable than a mixture
- CBD is not available as a pure compound. Children with epilepsies are administered medical cannabis with a ratio of CBD:THC of about 20:1 or less
- CBD is a nontoxic molecule which does not seem to cause side effects. However,the doses needed are high due low bioavailability
- Clinical trials are badly needed

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Raphael Mechoulam. J Basic Clin Physiol Pharmacol 2016; 27(3): 181–7